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Gastrointestinal motility and absorptive disorders in patients with inflammatory bowel diseases: Prevalence, diagnosis and treatment

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Abstract

Inflammatory bowel diseases (IBD), Crohn's disease and ulcerative colitis, are chronic conditions associated with high morbidity and healthcare costs. The natural history of IBD is variable and marked by alternating periods of flare and remission. Even though the use of newer therapeutic targets has been associated with higher rates of mucosal healing, a great proportion of IBD patients remain symptomatic despite effective control of inflammation. These symptoms may include but not limited to abdominal pain, dyspepsia, diarrhea, urgency, fecal incontinence, constipation or bloating. In this setting, commonly there is an overlap with gastrointestinal (GI) motility and absorptive disorders. Early recognition of these conditions greatly improves patient care and may decrease the risk of mistreatment. Therefore, in this review we describe the prevalence, diagnosis and treatment of GI motility and absorptive disorders that commonly affect patients with IBD.

Key words: Inflammatory bowel diseases; Crohn's disease; Ulcerative colitis; Gastrointestinal motility and absorptive disorders; Irritable bowel syndrome; Small intestinal bacterial overgrowth; Small intestinal fungal overgrowth; Dyssynergic defecation; Fecal incontinence; Chronic intestinal pseudo-obstruction

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Core tips: Gastrointestinal motility and absorptive disorders such as small intestinal bacterial overgrowth, carbohydrate malabsorption or dyssynergic defecation are highly prevalent in inflammatory bowel diseases (IBD) patients and often explain refractory symptoms in inactive disease. Prompt diagnosis of these conditions improves patient care and may decrease the risk of mismanagement in IBD population. In the present

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manuscript we provide a comprehensive review of the prevalence, diagnosis and the best management strategies of these disorders.

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INTRODUCTION

Inflammatory bowel diseases (IBD) including Crohn's disease (CD) and ulcerative colitis (UC) are chronic relapsing disorders that often require long-term therapy and follow up^[1,2]. They are recognized for their complex pathophysiology that involves innate immune system deregulation and altered microbiome in genetically predisposed individuals^[3].

Despite adequate treatment, a subgroup of IBD patients exhibit persistent gastrointestinal (GI) symptoms such as abdominal pain, dyspepsia, diarrhea, urgency, fecal incontinence (FI), constipation and bloating that are not always related to mucosal damage. In this setting, it is crucial to exclude superimposed conditions before reassessing degree of inflammation with further invasive diagnostic testing or escalating potentially harmful anti-inflammatory treatments.

GI motility disorder and IBD specialists are falling short of staying up-to-date in each field due to exceedingly sub-specialized nature of these disciplines as the two fastest growing fields of luminal gastroenterology. GI motility disorders are observed in more than one third of IBD patients, which significantly impair overall quality of life^[4,5]. Herein, we describe the prevalence, diagnosis and management of the most common GI motility disorders associated with IBD.

CONDITIONS WITH PERSISTENT NON-BLOODY DIARRHEA

An IBD flare may be recognized when patients present with rectal bleeding, mucus or tenesmus; however, non-specific GI symptoms such as diffuse abdominal pain or altered bowel habits do not always reflect a flare. Fecal calprotectin has been used as a surrogate biomarker for active inflammation in IBD and it is considered a reasonable instrument to predict response to therapy^[6,7]. Despite a 97% positive predict value to rule-in a flare, a negative result does not necessarily diagnose IBS or any other specific superimposed disease^[8]. Active small bowel inflammation can account for up to 10% of CD patients^[9]. Enteric stenosis and fistulas are not diagnosed by a routine colonoscopy and in these scenario non-invasive tests such as C-reactive protein and fecal calprotectin are not considered reliable markers. Current guidelines recommend cross-sectional imaging as magnetic resonance enterography, when available^[10]. Treatment for active disease demands therapy optimization either with escalation of anti-inflammatory drugs, such as immunomodulators and biologic agents or surgery. There are several conditions that should be excluded in an IBD patient presenting with persistent diarrhea despite relative control of inflammation. (Table 1 summarizes clinical presentations and Table 2 outlines the diagnostic and therapeutic approaches)

Celiac disease is more prevalent in IBD patients than in general population. A large systematic review with over 41000 patients from 17 studies has shown a 2-fold increase risk for Celiac disease. Overall, in IBD patients the prevalence of Celiac disease was 1110/100000 [95% confidence interval (CI), 1010-1210/100000] as compared to 620/100000 (95%CI, 610-630/100000) in general population^[11]. Screening is based on IgA anti-tissue transglutaminase, anti-endomysial antibodies and serum total IgA concentration. Both children and patients with total IgA deficiency should be tested with IgG anti-tissue transglutaminase or deamidated gliadin peptide. Positive serology can be further assessed with upper endoscopy with duodenal biopsies to evaluate villous atrophy and degree of inflammation^[12]. The standard therapy is a lifelong gluten-free diet^[13]. In underdeveloped countries giardiasis should be also ruled out, as a common parasitic infection which might mimic Celiac disease by causing diarrhea and bloating^[14]. Treatment is based on nitroimidazoles derivatives drugs or nitazoxanide^[15].

Table 1 Common symptoms of overlapping gastrointestinal disorders in inflammatory bowel disease patients

Disease	Symptoms
Bile-acid malabsorption	Diarrhea, urgency
Exocrine pancreatic insufficiency	Abdominal discomfort, bloating, diarrhea, greasy stools
Carbohydrates intolerance	Abdominal discomfort, bloating, diarrhea
Small intestinal bacterial overgrowth	Abdominal discomfort, bloating, constipation, diarrhea, distention, sensation of incomplete evacuation, urgency
Small intestinal fungal overgrowth	Abdominal discomfort, bloating, diarrhea, distention, urgency
Dyssynergic defecation	Abdominal discomfort, bloating, constipation, diarrhea, distention, sensation of incomplete evacuation, straining, urgency
Ehlers-Danlos syndromes-hypermobility type	Abdominal pain, bloating, constipation, distention, sensation of incomplete evacuation, straining, pelvic floor dysfunction
Mast cell activation syndrome	Abdominal discomfort, bloating, dynamic allergies, diarrhea, distention, sensation of incomplete evacuation, urgency
Eosinophilic gastroenteritis	Abdominal pain, bloating, diarrhea
Intra-abdominal adhesions	Abdominal pain, bloating, distention
Irritable bowel syndrome	Abdominal discomfort, bloating, diarrhea / constipation, distention, sensation of incomplete evacuation, urgency
Celiac disease	Abdominal discomfort, bloating, diarrhea
Giardiasis	Abdominal discomfort, bloating, diarrhea

Bile acid malabsorption (BAM) is another cause of persistent diarrhea especially in ileal CD or in patients with previous terminal ileal resection^[16,17]. Although not approved in United States, ⁷⁵selenium homotaurocholic acid test remains the gold standard for diagnosis of BAM. When available, other tests such as serum 7 α -hydroxy-4-cholesten-3-one (C4) and a 48-h fecal measurement of chenodeoxycholic and deoxycholic acids may be helpful for diagnostic workup^[18]. Indeed, in a pediatric IBD cohort, 23% (10/44) of CD patients with persistent non-bloody diarrhea had higher serum C4-concentrations when compared to controls^[19]. A short course of cholestyramine as a diagnostic tool to diagnose BAM is a reasonable approach when the above noted tests are not available. Treatment consists of bile acid sequestrants such as cholestyramine, colestipol, or colesevelam and a low-fat diet. Novel therapeutic targets as farsenoid X agonist have been studied with promising results, however randomized controlled trials are still lacking^[20]. While bile acid binders such as cholestyramine are the mainstay of treatment of BAM, caution should be used in IBD patients. They are known to block absorption of concomitant medications, which might be a concern for patients on 5-aminosalicylic acid, immunosuppressant or Janus kinase inhibitor therapies. Moreover, they can decrease serum liposoluble vitamins levels and fat absorption leading to worsening abdominal distention/bloating, steatorrhea and malnutrition.

Undiagnosed exocrine pancreatic insufficiency can also lead to diarrhea and fat malabsorption in IBD patients. Exocrine dysfunction should be considered at any age even in elderly, as older age correlates directly with reduced exocrine pancreatic function^[21]. In a cross-sectional study, the estimated incidence of exocrine pancreatic insufficiency in IBD patients, considering the cut-off of fecal elastase-1 level < 200 μ g/g, was 14% in CD and 22% in UC. Compared to controls, the odds ratio of exocrine pancreatic insufficiency was 8.34 (95%CI: 1.34-37.89) for CD and 12.95 (95%CI: 2.91-57.58) for UC patients. The risk was higher in patients with more than three bowel movements per day^[22]. Although uncommon, type-2 autoimmune pancreatitis has been also associated with IBD, which can lead to exocrine insufficiency^[23]. According to the International Consensus Diagnostic Criteria the diagnosis is based on imaging findings such as enlargement of the pancreas or narrowing of the main pancreatic duct, the presence of granulocyte epithelial lesions in histology, frequent association with extra-pancreatic involvement and considerable response to steroids. In contrast with type-1 autoimmune pancreatitis, serum IgG4 is not elevated^[24].

From the clinical perspective, steatorrhea is expected only at end-stage pancreatic insufficiency. Less severe disease usually manifests as watery diarrhea and weight loss. The diagnosis relies on the clinical suspicion and on the determination of indirect pancreatic function tests. Fecal elastase is widely accessible, easy to perform and recommended by the American Pancreatic Association for diagnosis^[25]. This test has been shown to have a pooled sensitivity of 77% and 88% of specificity when

Table 2 Causes of irritable bowel syndrome-like symptoms in inflammatory bowel disease patients

Disease	Diagnosis	Treatment
Small bowel CD	Computed tomography or magnetic resonance enterography	Drug escalation or surgery
Bile-acid malabsorption	⁷⁵ SeHCAT, 48-hour fecal bile acids, trial with bile acid binders	Bile acid sequestrants
Exocrine pancreatic insufficiency	Fecal elastase ¹ , trial with pancreatic enzymes	Pancreatic enzyme replacement
Carbohydrates intolerance	Hydrogen breath test	Dietary restriction
Small intestinal bacterial overgrowth	Lactulose or glucose breath tests: rise from baseline in H ₂ ≥ 20 ppm within 90 min or CH ₄ ≥ 10 ppm	H ₂ : Rifaximin, doxycycline or amoxicillin CH ₄ : Rifaximin and neomycin, or rifaximin and metronidazole, or amoxicillin-clavulanate or ciprofloxacin and metronidazole
Small intestinal fungal overgrowth	Quantitative culture of intestinal aspirate ≥ 10 ³ CFU/mL	Anti-fungal therapy (<i>e.g.</i> , fluconazole)
Dyssynergic defecation	Anorectal manometry with balloon expulsion test, defecography	Biofeedback behavior therapy
Ehlers-Danlos syndrome-hypermobility type	Beighton score ≥ 4 ^[105] and arthralgia, erect barium testing for visceroptosis	Pelvic physiotherapy, promotility agents
Mast cell activation syndrome	Typical symptoms, elevated mast cell mediators (<i>e.g.</i> , tryptase) and response to mast cell stabilizing agents	H1 blockers, H2 blockers, cromolyn sodium, referral to hematologist/allergist
Eosinophilic gastroenteritis	Eosinophilic infiltration on pathology	Anti-inflammatory agents
Intra-abdominal adhesions	Clinical history, previous history of adhesions	Consideration of surgical lysis of adhesions
Giardiasis	Detection of <i>Giardia lamblia</i> antigens in stool	Metronidazole or nitazoxanide
Celiac disease	IgA anti-tissue transglutaminase and serum total IgA, EGD with duodenal biopsies	Gluten-free diet

¹False-positive results are observed in liquid stools. CD: Crohn's disease; ⁷⁵SeHCAT: Selenium-75-homocholeic acid taurine scan; CFU: Colony-forming unit; H1: Histamine 1 receptor; H2: Histamine 2 receptor; EGD: Esophagogastroduodenoscopy.

compared to secretin stimulation test in a recent meta-analysis^[26]. However, false-positive results are observed in patients with chronic watery diarrhea and, therefore, this test might not be as reliable for the IBD population^[26]. A trial of pancreatic enzyme replacement is reasonable and safe option for treatment in the context of exocrine dysfunction in IBD.

Although IBD associated inflammation can potentially lead to decreased mucosal disaccharidases, data on the true rate of sucrose/lactose intolerance in IBD patients is scarce. Physicians should be vigilant about possibility of carbohydrate intolerance (*i.e.*, lactose, sucrose and fructose) in IBD patients. Apart from correlation of dietary items with symptoms, hydrogen breath testing can be used to make the diagnosis^[27]. Presence of small intestinal bacterial overgrowth (SIBO) must be ruled-out prior to breath testing for carbohydrate malabsorption as SIBO leads to a positive fructose/sucrose/lactose breath test in up to one third of patients^[27]. Treatment is instituted by avoiding the carbohydrate, preferable with the help of a dietician.

Mast cell activation syndrome (MCAS) is a chronic multisystem disease of abnormal mast cell degranulation secondary to regulatory gene mutations leading to inappropriate release of mast cell mediators. MCAS has been described recently in 2007 and our understanding on how to diagnose and treat the disease is rapidly evolving^[28]. MCAS can affect multiple organs including cardiovascular, GI, dermatologic, hepatic, neurologic and musculoskeletal systems. GI manifestations include nausea, heartburn, abdominal pain, and altered bowel habits^[29]. If suspected, treatment with antihistamines (H1 and H2 blockers), cromolyn sodium or disodium cromoglycate may be beneficial, however, referral to an allergist or hematologist familiar with treatment of MCAS is indispensable in management of these patients^[30].

Eosinophilic gastroenteritis is a rare Th2-type mediated disease which is believed to be induced by food or environmental allergens^[31,32]. To the best of our knowledge there is no data in the literature that have addressed primary eosinophilic gastroenteritis in IBD. Nonetheless, in general population the estimated prevalence is 5 in 100000 inhabitants and it appears to be more frequent in males and young adults^[33]. Symptomatology may range from abdominal pain, bloating or diarrhea to protein losing enteropathy and malnourishment^[34]. The presence of GI symptoms and histopathological findings of a dense eosinophilic infiltration, eosinophilic cryptitis or abscesses confirms the diagnosis^[35]. Peripheral eosinophilia is commonly observed despite not being mandatory for diagnosis. In addition, some reports have

documented anecdotal cases of eosinophilic gastroenteritis induced by anti-tumor necrosis factor in IBD patients^[36,37]. Amongst first-line therapeutic options are a short trial of elemental diet (with the goal of eliminating food antigen exposure) and systemic corticosteroids^[31]. Recently, Grandinetti *et al*^[38] have reported promising histological improvement in refractory patients treated with vedolizumab, a monoclonal antibody against $\alpha 4\beta 7$ integrin. However, further evidence of clinical efficacy is needed.

Intra-abdominal adhesions are highly prevalent in IBD daily practice as colectomy and small bowel resections are required in up to 10% of UC and approximately 30% of CD patients during the lifetime^[39,40]. Furthermore, adhesions caused by fistulas, endometriosis and non-GI abdominal surgeries can also occur in IBD patients. The estimated prevalence of intra-abdominal adhesions in IBD population is lacking. Postprandial abdominal pain, bloating, distension, nausea and alternating bowel habits are the most common clinical presentation^[41]. A past medical history of abdominal surgery heightens a diagnostic suspicion of adhesions. Conservative management with fasting, intravenous hydration and/or a nasogastric tube is generally the first choice of treatment, whereas surgical lysis should be indicated for refractory cases^[42]. IBS, SIBO and small intestinal fungal overgrowth (SIFO) can also lead to chronic diarrhea, which are described in detail below.

IBD/IRRITABLE BOWEL SYNDROME OVERLAP

Irritable bowel syndrome (IBS) is one of the most prevalent differential diagnoses in IBD population with refractory symptoms which significantly impact patient-reported outcomes. A number of studies have demonstrated higher prevalence of IBS in quiescent IBD patients than general population. The largest published meta-analysis, including over 1700 subjects, estimated a 4-fold increase in prevalence of IBS in IBD patients when compared to the general population (OR 4.39; 95% CI 2.24-8.61). The pooled prevalence of IBS in both UC and CD patients during clinical remission was 31% and 41%, respectively. There was significant heterogeneity between the studies with various criteria used to define remission and IBS^[43]. Moreover, the majority of these studies did not vigorously rule-out alternative causes of IBS-like symptoms, therefore the exact prevalence of IBS in IBD patients remains unclear.

The current accepted hypothesis states that IBD-IBS patients exhibit an enhanced neuronal responsiveness due to chronic inflammation with subsequent visceral hypersensitivity, hyperalgesia, allodynia, dysmotility and altered intestinal secretions^[44]. Vivinus-Nebot *et al*^[45] found that IBS symptoms in quiescent IBD subjects are associated with ongoing microscopic inflammation, increased paracellular permeability, intraepithelial lymphocytosis and high TNF- α levels. Conversely, tight junctions' proteins such zonulin and alfa-catenin were decreased. Akbar *et al*^[46] have demonstrated that IBS symptoms were secondary to prior inflammatory changes as shown by the correlation of abdominal pain scores with the upregulation of visceral hypersensitivity receptor in IBD-IBS patients.

As the Rome criteria for diagnosis of IBS are based on clinical symptoms, they may not serve as an appropriate diagnostic tool in IBD patients which may exhibit similar symptoms^[47]. Biomarkers are desperately needed to objectively rule-in IBS. Recently, Pimentel *et al*^[48] have validated two autoantibodies derived from the underlying pathophysiology of post-infectious IBS. In a large cohort of 2823 patients, higher levels of anti-cytolethal distending toxin B (CdtB) and anti-vinculin were detected in IBS patients as compared to IBD patients and healthy controls. Anti-CdtB had a specificity and sensitivity of 91.6% and 43.7% and anti-vinculin showed specificity and sensitivity of 83.8% and 32.6%, respectively to rule-in IBS as compared to IBD. Given the high specificity but modest sensitivity of these tests, a positive result rules in post-infectious IBS but a negative result does not rule out IBS. The role of these biomarkers in IBD patients with overlapping IBS is yet to be determined.

A comprehensive multi-disciplinary treatment approach includes a combination of enhanced physician-patient relationship, dietary changes and medications^[49,50]. A meta-analysis has demonstrated significant benefit of low-FODMAPs (fermentable oligosaccharides, disaccharides, monosaccharides, and polyols) diet in improving functional GI symptoms in IBS and IBD patients^[51]. If this diet is initiated, it is crucial to reintroduce FODMAPs foods after 4-6 wk to achieve a less restrictive personalized diet^[52]. Neuromodulators and behavioral therapies have been advocated in treatment of IBS symptoms^[53]; however, the role of these interventions is yet to be elucidated in IBD-IBS overlap. Currently, lubiprostone, plecanatide and linaclotide are approved for treatment of IBS-Constipation while rifaximin, eluxadolone and alosetron are approved for IBS-D by Food and Drug administration (FDA) in the United States^[54]. It

should be noted that IBD patients were excluded from the trials assessing these drugs. While alosetron is contraindicated in patients with IBD, eluxadoline is contraindicated in patients with previous cholecystectomy and can cause pancreatitis, which limits their use in IBD population^[55,56].

SMALL INTESTINE BACTERIAL OVERGROWTH

SIBO is a common disease associated with a variety of diseases with altered gut motility, including diabetes, intestinal pseudo-obstruction, scleroderma, IBS and IBD. It is characterized by overproliferation of colonic bacteria in the small bowel and enhanced release of gases as a consequence of carbohydrate fermentation^[57]. Predisposing factors for SIBO in IBD population may be seen in the setting of small bowel dysmotility, enteric-colonic fistula tract, stenosis, abdominal surgery, exocrine pancreatic dysfunction or ileocecal resection.

Major complaints are bloating, abdominal distension, abdominal discomfort, flatulence, diarrhea and/or constipation. Methane-predominant (*i.e.*, overgrowth of methanogenic archaea) bacterial overgrowth commonly manifests as constipation whereas hydrogen and hydrogen sulfide-predominant SIBO patterns are usually seen in the setting of diarrhea and rectal urgency^[58]. Severe forms of SIBO may provoke small bowel villous atrophy, malabsorption, liposoluble vitamins deficiency, hypoalbuminemia and eventually weight loss.

The gold standard test for the diagnosis is presumed to be small bowel aspirate culture with $\geq 10^3$ bacterial colony forming units (CFU)/mL (formerly 10^5 CFU/mL)^[27]. Nevertheless, current small bowel sampling techniques are time-consuming, costly and bear the risk of contamination with oral flora. Moreover, it is rather near-sighted to assume that a sample from a 5-cm segment of jejunum or duodenum would represent the whole 20 feet of small bowel. In the current clinical practice SIBO is diagnosed by lactulose or glucose breath testing^[59]. The North American Consensus defines a positive result as rise in hydrogen ≥ 20 ppm during the test or by 90 min, whereas a level of ≥ 10 ppm is positive for excess methane^[27]. Not uncommonly, IBD patients require broad-spectrum antibiotic therapy in the setting of perianal CD, pouchitis or for prevention of postoperative recurrence^[60]. Breath testing for diagnosis of SIBO should be deferred for 4 wk after antibiotic therapy. Empiric treatment with antibiotics as a diagnostic method should be discouraged for the potential risk of drug resistance and *Clostridioides difficile* infection in already immunosuppressed patients.

A meta-analysis of 11 studies with over 1500 subjects has found greater prevalence rates of SIBO in IBD group compared to controls. Diagnosis was established by breath tests and glucose was the most common substrate used. Overall prevalence was 22.3% (262/1175), 25.4% (95%CI: 22.5-28.3) in CD and 14.3% (95%CI: 10.52-18.08) in UC patients. Pooled odds ratio from 5 case-controls studies was 9.51 (95%CI: 3.39-26.68). Descriptive subanalysis showed a positive correlation between SIBO and worsening of abdominal symptoms such as bloating, flatus, satiety and loose stools. However, no association was found with disease duration, activity or immunosuppressant therapy^[61].

The largest epidemiologic study of SIBO comes from a single center database of 14847 breath tests performed between 2005 and 2013, including 486 IBD and 10505 non-IBD patients^[62]. Lactulose was the substrate used and the cutoff points were in accordance with published guideline on SIBO. Bloating and abdominal distension were the most common indications for testing. Prevalence of SIBO in IBD patients with ongoing GI symptoms was 56.8%. CD and UC patients showed similar prevalence rates. H₂-predominant pattern was the most frequent result in IBD and non-IBD groups, while IBD subjects produced less methane than controls, excess methane production in IBD patients was associated with constipation.

SIBO is generally treated with antibiotic therapy. Good response rates are observed in both non-IBD and IBD patients, although limited data are available for the latter^[63]. In a meta-analysis of 32 studies with 1331 patients with SIBO rifaximin treatment was effective and safe, with overall eradication rate of 70.8% (95%CI: 61.4-78.2), in an intention-to-treat analysis. Furthermore, 67.7% of patients (95%CI: 44.7-86.9) reported either improvement or resolution of GI symptoms after treatment^[64]. Gu *et al*^[62] described that 57.3% out of 117 IBD patients diagnosed with SIBO responded to antibiotic therapy, without a significant differences between the response rate of CD and UC patients.

Rifaximin, doxycycline or amoxicillin are first line treatment for hydrogen-predominant SIBO, while excess methane producers can be treated with combination antibiotic therapy of rifaximin and neomycin, or rifaximin and metronidazole, or

amoxicillin-clavulanate or ciprofloxacin and metronidazole^[63]. Patients need to be counseled regarding the high rate of recurrence of SIBO after therapy. In non-IBD patients, SIBO has also been treated with a 2-3 week course of elemental diet with success rate of 70%-90%^[65]. This is an interesting concept as elemental diet can also be used in treatment of IBD^[66]. Hence, this option can be considered in IBD patients with refractory disease who also suffer from SIBO.

SMALL INTESTINAL FUNGAL OVERGROWTH

SIFO was first suggested as a pathologic condition four decades ago and recently defined by excess fungi proliferation in the small bowel, particularly *Candida* sp. Immunocompromised patients with HIV infection, diabetes or malignancy are at higher risk for SIFO^[67]. SIFO has been associated with IBS-like symptoms and its clinical presentation may be indistinguishable from SIBO. The reported prevalence of SIFO was 26% of 150 subjects evaluated for chronic GI complaints, most frequently abdominal pain, bloating, flatulence or diarrhea^[68].

A prospective study has demonstrated higher rates of SIBO or SIFO in patients who had undergone previous colectomy. The most common indications for colectomy were colonic inertia, cancer, diverticular disease, bowel obstruction and CD in 6% of them (3/50). However, no significant differences were seen on symptomatology after treatment between positive and negative groups^[69].

Although data are lacking, theoretically, it would be important to address SIFO in IBD patients as they are often immunosuppressed, use broad-spectrum antibiotics and commonly undergo abdominal surgery. The diagnostic workup requires an upper endoscopy with a sterile collection of small intestinal aspirate from the distal duodenum or proximal jejunum $\geq 10^3$ CFU/mL of fungal growth is proposed as a positive result^[70].

When the diagnosis is made, Erdogan *et al*^[70] suggest a two to three weeks course of anti-fungal therapy (*e.g.*, fluconazole). Echinocandins and amphotericin B are reserved for invasive candidiasis and for treatment of *Candida glabrata* and *Candida krusei*^[70]. Future research is needed to better position SIFO into GI functional disorders.

CONSTIPATION

The prevalence of constipation in IBD patients appears to be similar to the general population^[71]. Farrokhyar *et al*^[72] assessed 149 patients with inactive IBD and found that constipation was present in 10.7% of patients. UC patients had higher rate of constipation as compared to CD (25% *vs* 5.7%). Assessment of constipation involves a comprehensive review of medical history and current medications to exclude secondary causes. In IBD patients, colorectal cancer is major a concern when addressing recent-onset constipation.

Non-pharmacological interventions such as exercise, increased fluid intake or soluble fiber have modest efficacy in general population and may be considered in IBD patients. Polyethylene glycol, an osmotic laxative, is the first line drug to treat constipation. Prucalopride and tegaserod are selective serotonin type 4 agonists which are recently approved/reintroduced by FDA for treatment of constipation^[73]. Safety of these medications is yet to be determined in the IBD population^[74].

Secretagogues are also effective in treatment of constipation. In a recent meta-analysis, linaclotide, lubiprostone and plecanatide were all shown to be superior to placebo in treatment of constipation. The most common side effects were diarrhea and nausea^[75]. Experimental studies have suggested that some prosecretory agents exhibit anti-inflammatory properties and could potentially be candidates for the treatment of IBD. Plecanatide and dolcanatide, both guanylyl cyclase C agonists, improved colitis in mice by downregulation of pro-inflammatory cytokines and their effect was comparable to 5-amino salicylic acid^[76]. Moreover, a small trial with 28 subjects found that lubiprostone, a chloride channel activator, decreased intestinal permeability in healthy volunteers^[77]. Potential anti-inflammatory effects of secretagogues make them an intriguing option for treatment of constipation in IBD patients.

One other differential diagnosis to consider for constipation and IBS-like symptoms in IBD patients is Ehlers-Danlos Syndrome (EDS). EDS is a heterogeneous group of heritable connective tissue disorders and are grossly underdiagnosed. EDS type III (hypermobility type) is the most common type and is associated with significant GI symptoms such as constipation, straining, abdominal pain, nausea, distention, pelvic floor dysfunction, heartburn, and IBS-like symptoms^[78]. Diagnosis of EDS III is entirely clinical without any objective or genetic testing^[79]. The pathophysiology of GI

symptoms in EDS patients remains unknown but visceroptosis, defined as prolapse of abdominal organs below their natural position, has been proposed as the cause of GI symptoms in EDS. Therapy is symptom-directed and involves a multidisciplinary approach. Physiotherapy and promotility drugs have been indicated to treat GI symptoms in these groups of patients but clinical trials are lacking.

DYSSYNERGIC DEFECTION

Dyssynergic defecation (DD) is a well-known cause of chronic constipation; however, in IBD patients it can also manifest with rectal discomfort, sensation of incomplete evacuation, diarrhea or FI^[80]. DD is characterized by the discoordination between the contraction of abdominal wall and pelvic floor muscles that prevents adequate evacuation.

IBD patients have an increased risk of DD due to chronic changes in bowel habits, perianal disease and surgical procedures^[81]. Previous studies have reported IBD to be associated with sensorimotor anorectal function, increased anal pressure, increased rectal sensitivity and absent rectoanal inhibitory reflex^[81,82]. In a recent meta-analysis we have found a high prevalence rate from 45% to 97% in 2 studies with 182 IBD patients with ongoing GI symptoms^[83].

Diagnosis of DD in IBD patients is generally made based on anorectal manometry with a balloon expulsion test. Magnetic resonance/barium defecography and anal sphincter electromyography can also be utilized^[83]. For the last three decades biofeedback has been the standard treatment for DD and previous studies have reported high symptomatic response, reduced healthcare utilization and improved overall quality of life. We have shown a response rate of 86% and 70% in patients with and without ileal pouch anal anastomosis (IPAA), respectively^[83]. IBD patients with anal stricture, fissure and stenosis may have limited benefit from biofeedback therapy. Invasive procedures such as botulinum toxin injection are not recommended for IBD patients considering the increased risk of perianal fistula and FI.

FECAL INCONTINENCE

FI is a commonly neglected symptom in IBD and is not infrequent to be referred as frequent bowel movements, urgency or tenesmus. FI is defined as involuntary fecal loss of liquid or stool. Several reports have shown FI to have a significant negative impact on physical, social and emotional state of IBD patients^[84,85].

FI prevalence has been underestimated over the last decades due to social stigma, patient's embarrassment and inadequate medical awareness. In a recent meta-analysis, we have found that pooled prevalence of FI in IBD patients is 37% (95% CI: 12%-62%). IBD patients have a higher chance of having FI as compared to non-IBD subjects (OR 7.73, 95% CI: 6.3-9.9). Rate of FI was similar among UC and CD patients. Higher risk of FI in IBD patients is likely due chronic changes in bowel habits, perianal disease/surgeries, loss of rectoanal inhibitory reflex and abnormal rectal sensation^[86].

Diagnosis of FI requires a complete perianal examination, including inspection during Valsalva's maneuvers and digital rectal exam to evaluate sphincter tone at rest and squeeze. Anorectal manometry is the gold standard to assess anorectal function, compliance, reflexes and sensation. In cases of suspected rectocele or anal sphincter defect further diagnostic testing with endoanal ultrasound and defecography might be considered^[82].

Initial management includes better control of diarrhea if present. Antidiarrheal drugs such as loperamide or diphenoxylate can be used as needed. Increasing fiber intake or bulking agents in IBD may be complicated with bloating and abdominal distention. Biofeedback therapy has been proven to be effective in IBD patients. In a retrospective cohort, almost 80% of patients showed improved symptoms irrespective prior perianal fistula, IPAA or past obstetric trauma^[87].

Sacral nerve stimulation is an FDA approved option for refractory FI with excellent results in non-IBD patients. Limited case series have reported positive response in IBD subjects^[88,89]. One study has shown that concomitant treatment with infliximab and surgical repair improved and maintained long-term continence in perianal CD patients^[90]. Anecdotal studies with percutaneous tibial nerve stimulation and pneumatic dilatation of the rectum have been done, but small sample size limits us to draw meaningful conclusions^[91,92]. Injecting agents such as dextranomer gel and surgical procedures are contraindicated for IBD patients due to the risk of perianal abscess and fistula formation. Diverting loop colostomy could be acceptable when all

above-mentioned therapies have failed.

CHRONIC INTESTINAL PSEUDO-OBSTRUCTION

Chronic intestinal pseudo-obstruction (CIPO) is a severe motility disorder characterized by obstructive symptoms in an otherwise patent GI tract^[93]. Although rare, the early recognition of its clinical presentation might provide safe and effective therapeutic measures to improve the quality of life. In a large cohort of CIPO patients, 84% of them required surgery, 76% were dependent on home parenteral nutrition and the survival rate was 68% in over a ten-year period of follow-up^[94]. Non-specific symptoms such as abdominal pain or distension are the most frequently reported at initial stage and it is not uncommon for patients to be misdiagnosed with IBS. Nausea, vomiting, constipation and malabsorption occur with disease progression, whereas diarrhea is generally a consequence of superimposed SIBO.

The pathophysiology generally includes myopathy, neuropathy or dysfunctional interstitial cells of Cajal^[95,96]. Apart from neurologic and autoimmune diseases, small bowel CD is an important underlying cause of CIPO and should be ruled out prior to establishing proper treatment. There are few case reports in the literature of CD mimicking CIPO. These patients presented with refractory diarrhea, electrolyte disturbances and malnourishment^[97,98]. Diagnosis of CIPO can be challenging. Laboratory tests may distinguish primary from secondary causes, while upper endoscopy and colonoscopy assess mechanical obstruction. Computed tomography or magnetic resonance can elaborate dilation of bowel loops. Antroduodenal manometry can confirm myogenic/neurogenic dysmotility, although access is limited and is only available in selected centers^[99].

Effective treatments for CIPO are lacking. Nutritional support is required and patients should be advised to increase protein. Elemental diet and enteral nutrition might also be needed. Pharmacological therapy with prokinetics such as erythromycin, domperidone or prucalopride may be effective but should be discontinued if it fails after a short trial. Peripherally acting mu-opioid receptor antagonist, gabapentin, pregabalin, tricyclic antidepressants, serotonin and norepinephrine reuptake inhibitors can be prescribed for pain control with considerable side effects. Opioids should be avoided. Treating concomitant SIBO may improve diarrhea and distension^[100,101].

Surgery is no longer indicated and refractory patients might benefit from percutaneous endoscopic gastro-jejunostomy (PEG-J). A pilot study has evaluated the efficacy of PEG-J decompression in 7 patients diagnosed with CIPO and found a marked improvement in serum albumin, oral intake and abdominal symptoms. No major adverse events were reported, except for reflux chemical dermatitis^[102].

Intestinal transplant (isolated or multivisceral) is considered a salvage therapy for intractable CIPO and CD patients who present with complications of parenteral nutrition. Up until 2015, over 2500 patients had undergone intestinal transplant worldwide with a survival rate of 76% and 43% in one and ten years, respectively^[103]. Despite transplant, a subgroup of patients with dysmotility might still requires end ileostomy for symptomatic improvement^[104].

CONCLUSION

Motility and absorptive disorders are highly prevalent in IBD patients, particularly in those with persistent GI symptoms despite quiescent disease. Timely diagnosis and appropriate treatment of these conditions significantly improves care and well-being of IBD patients. Despite the high prevalence and significant impact of these disorders in IBD patients, evidence in diagnosis and treatment is critically lacking. Future controlled studies are needed to address motility and absorptive disorders specially in IBD patients.

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